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## Articles

# Impact of Reduced Heart Rate Variability on Risk for Cardiac Events

## The Framingham Heart Study

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## Abstract

**Background** Although heart rate variability (HRV) is altered in a variety of pathological conditions, the association of reduced HRV with risk for new cardiac events has not been studied in a large community-based population.

**Methods and Results** The first 2 hours of ambulatory ECG recordings obtained on subjects of the Framingham Heart Study who were free of clinically apparent coronary heart disease or congestive heart failure were reprocessed to assess HRV. Five frequency-domain measures and three time-domain measures were obtained. The associations between HRV measures and the incidence of new cardiac events (angina pectoris, myocardial infarction, coronary heart disease

death, or congestive heart failure) were assessed with proportional hazards regression analyses. There were 2501 eligible subjects with a mean age of 53 years. During a mean follow-up of 3.5 years, cardiac events occurred in 58 subjects. After adjustment for age, sex, cigarette smoking, diabetes, left ventricular hypertrophy, and other relevant risk factors, all HRV measures except the ratio of low-frequency to high-frequency power were significantly associated with risk for a cardiac event ( $P=.0016$  to  $.0496$ ). A one-standard deviation decrement in the standard deviation of total normal RR intervals (natural log transformed) was associated with a hazard ratio of 1.47 for new cardiac events (95% confidence interval of 1.16 to 1.86).

**Conclusions** The estimation of HRV by ambulatory monitoring offers prognostic information beyond that provided by the evaluation of traditional cardiovascular disease risk factors.

**Key Words:** heart rate • electrocardiography • prognosis • epidemiology

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## Introduction

Heart rate variability, or heart period variability, is a measure of the cyclic variations of beat-to-beat (RR) intervals that reflects cardiac autonomic function.<sup>1</sup> Heart rate variability is influenced by various physiological and pathological conditions.<sup>2 3 4 5 6 7 8 9 10 11 12 13</sup> For several decades, obstetricians have recognized diminished beat-to-beat variation in fetal heart rate as an indicator of distress.<sup>14</sup> In cardiology, prior studies have documented adverse prognostic implications of reduced heart rate variability in patients after myocardial infarction<sup>15 16 17</sup> and with other pathological conditions.<sup>18 19 20 21</sup> Recently, we reported<sup>22</sup> an association between reduced heart rate variability and risk for all-cause mortality in elderly original participants in the Framingham Heart Study. The relation of altered heart rate variability to risk for cardiac events has not been studied in the general population.

The present investigation was undertaken to examine the association of reduced heart rate variability with risk for cardiac events in a large population-based sample. Subjects in this study included elderly participants in the original Framingham Heart Study and younger participants in the Framingham Offspring Study. The study setting provides an opportunity to explore the prognostic implications of heart rate variability measures in a sample in which referral bias is inherently minimal.

## ► **Methods**

### **Setting**

The Framingham Heart Study began in 1948, enrolling 5209 residents of Framingham, Mass, who were between the ages of 28 and 62 years in a prospective epidemiological study. In 1971, 5124 subjects (offspring of the original cohort and spouses of these offspring) were entered into a second prospective study. Selection criteria and study design have been reported previously.<sup>23 24 25</sup> From 1983 to 1987, ambulatory ECG recordings were obtained routinely on original Framingham Heart Study subjects undergoing their 18th biennial examination and Framingham Offspring Study subjects attending their 3rd examination.

### **Processing of Ambulatory Recordings**

All ambulatory recordings included two channels of ECG information and were obtained on standard four-track cassette tapes with the use of either a Cardiodata PR2 or PR3 pace recorder (Cardiodata Corp). The tape speed was 1 mm/s, and one channel was used to record a 32-Hz crystal-controlled timing track. For heart rate variability analysis, tapes were played back at 120 times real time on a Cardiodata/Mortara Mk5 Holter analysis system (Mortara Instrument Co) that sampled each ECG channel at 180 samples/s. The playback incorporated a phase-locked loop that used the recorded timing track to compensate for errors in recorder speed control. Because clinic examinations typically lasted 2 to 3 hours, only the first 2 hours of data were analyzed for heart rate variability by use of recently described methods.<sup>22</sup> Briefly, the fast Fourier transform was calculated on 100-s blocks of RR interval data. The power density spectrum was estimated by taking the sum of the squares of the magnitude of the fast Fourier transform performed on all usable 100-s blocks.<sup>26</sup> The resulting 100-s power spectra were corrected for attenuation. We computed power spectral densities on all usable 100-s blocks and calculated five frequency-domain measures: (1) very-low-frequency power (0.01 to 0.04 Hz), (2) low-frequency power (0.04 to 0.15 Hz), (3) high-frequency power (0.15 to 0.40 Hz), (4) total power (0.01 to 0.40 Hz), and (5) the ratio of low-frequency to high-frequency power.<sup>3</sup> In addition, we computed three time-domain measures: (1) the SD of normal RR intervals (2-hour SDNN), (2) the percentage of differences between adjacent normal RR intervals exceeding 50 ms (pNN50), and (3) the square root of the mean of the squared differences between adjacent normal RR intervals (r-MSSD).

Normal QRS complexes and arrhythmias were diagnosed under constant visual monitoring. Supraventricular premature beats were differentiated from sinus arrhythmia on the basis of P-wave morphology and cyclic changes in RR intervals.

### **Clinical Covariates**

Risk factors possibly predisposing to coronary heart disease were recorded at each examination.<sup>23</sup> Additional variables that might be associated with autonomic function also were considered, including coffee and alcohol consumption.

Systolic and diastolic blood pressures were measured twice on seated subjects by the examining physician using a mercury column sphygmomanometer positioned near eye level. The averages of repeated measures were used for analysis. Diabetes was defined, with the use of current and historical data, as a nonfasting blood glucose level  $\geq 200$  mg/dL ( $\geq 11.10$  mmol/L) or the use of insulin or an oral hypoglycemic agent. The diagnosis of left ventricular hypertrophy on the 12-lead ECG was made on the basis of fulfillment of at least one of the following voltage criteria with associated ST-T repolarization abnormalities: R wave  $> 1.1$  mV in aVL, R wave  $\geq 2.5$  mV in left precordial leads, S wave  $\geq 2.5$  mV in right precordium, sum of precordial SV<sub>1</sub> or SV<sub>2</sub> plus RV<sub>5</sub> or RV<sub>6</sub>  $\geq 3.5$  mV, or sum of limb lead RI plus SIII  $\geq 2.5$  mV. Current cigarette smoking status and use of cardioactive medications were recorded. For Offspring Study subjects, total and HDL cholesterol data were obtained at the index examination. Because total and HDL cholesterol data were not obtained at the 18th biennial examination of the original cohort subjects, levels obtained at a prior examination cycle 6 years earlier were used. Mean heart rate was calculated from the same ambulatory monitoring recording processed for the analysis of heart rate variability. The number of ventricular premature beats per hour was analyzed as a continuous variable, but supraventricular premature beats were categorized into three groups as follows:  $< 120$  per hour, 120 to 240 per hour, and  $> 240$  per hour. Average reported alcohol consumption was converted to ounces of alcohol per week on the basis of a published algorithm.<sup>27</sup>

### **Sample Selection**

At baseline, all study subjects had to be free of clinically apparent coronary heart disease and congestive heart failure by history and clinical examination. We required that they have  $\geq 60$  minutes of analyzable data<sup>16 17</sup> on the ambulatory recording, at least 50% time processed, and premature beats  $< 10\%$  of total beats.<sup>28</sup> Subjects were excluded if they had no follow-up contact after the index examination.

### **Outcome Events**

At each follow-up examination, interim cardiovascular events were assessed with the help of medical history, physical examination, and 12-lead ECG. Medical records were obtained for all participants, including those who did not attend an examination, and these were evaluated for evidence of interim heart disease. All suspected interim events were reviewed by a committee of three physicians who evaluated pertinent medical records, hospitalization records, and pathology reports. All deaths were evaluated by a committee of three physicians who determined probable cause after review of hospital records, autopsy findings, death certificates, and interviews with family members. A death that occurred within 1 hour of the onset of symptoms suggestive of coronary heart disease was classified as a sudden death attributable to coronary heart disease. A

death that occurred >1 hour after the onset of symptoms suggestive of myocardial ischemia was classified as a nonsudden death of coronary heart disease.

The primary end point in the present study was time to onset of coronary heart disease or congestive heart failure. Coronary heart disease comprised angina pectoris, coronary insufficiency (unstable angina with transient ischemic ECG changes), myocardial infarction (clinically recognized at time of occurrence or unrecognized), and sudden or nonsudden death attributed to coronary heart disease. Criteria for the cardiovascular disease events have been reported.<sup>29</sup>

### Statistical Methods

Measures of heart rate variability were transformed by natural logarithm because their distributions were skewed. Proportional hazards regression procedures<sup>30</sup> were used to assess heart rate variability measures as predictors of cardiac events. All proportional hazards regression analyses were stratified by sex with age as a covariate, and all were performed with the use of the Statistical Analysis System version 6.09 procedure PHREG<sup>31</sup> on a Sun Sparc 2 workstation.

Measures of heart rate variability were studied first without, then with adjustment for several pertinent clinical variables that may be associated with heart rate variability and/or subsequent cardiac events. These clinical variables included frequent supraventricular premature beats (<120/h versus  $\geq 120$ /h), systolic blood pressure (in mm Hg), left ventricular hypertrophy on ECG (no versus yes), diabetes (no versus yes), diuretic use (no versus yes),  $\beta$ -blocker use (no versus yes), other cardiac medication use (no versus yes), and cigarette smoking (no versus yes). These covariates were chosen by use of a stepwise procedure (selection criterion  $P < .20$ ) from a list that also included the following variables that were not selected ( $P \geq .20$ ): coffee consumption, alcohol consumption, diastolic blood pressure, starting time of day of recording, and ventricular premature beats. Mean heart rate was considered separately both because it had an inverse association with heart rate variability measures<sup>22</sup> and because mean heart rate reflects autonomic balance. Additional multivariate analyses were performed with the use of total cholesterol and the ratio of total to HDL cholesterol levels.

Separate analyses were performed for each measure of heart rate variability to assess its relations to the incidence of cardiac events. Events rates, expressed per 1000 person-years of follow-up, were computed for sex-specific tertiles of each heart rate variability measure. In addition, because the risk was assumed to be smooth and monotonic, risk was assessed as a function of continuous values for each heart rate variability measure. Hazard ratios and 95% CIs were computed for each heart rate variability measure, and the statistical significance level was  $P = .05$  (two-sided) for each significance test. As expressed, the hazards ratios represent the proportional increase in risk that is associated with having measured heart rate variability lower, by 1 SD, relative to an individual of the same sex with otherwise identical risk factors.



## Results

There were 5698 subjects who attended the index examination. A total of 2278 subjects did not have ambulatory ECG data (did not have an examination in the Framingham Heart Study clinic, ambulatory recording not obtained, poor quality recording, no available data, or missing tape). Among 3420 tapes analyzed, a total of 919 subjects were excluded for reasons listed in Table 1 ✦; arrhythmia or excessive artifact were the major reasons (n=666) for exclusion. Compared with ineligible subjects, the eligible subjects were younger, had lower blood pressure, and had more favorable clinical risk factors. The eligible sample of 2501 subjects comprised 1101 men and 1400 women. Their clinical characteristics are shown in Table 2 ✦. The mean age was 52 years for men and 54 years for women. Women had higher HDL cholesterol levels, a lower ratio of total to HDL cholesterol, lower diastolic blood pressure, and higher mean heart rate than men.

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**View this table:** **Table 1.** Evaluable Cases

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**View this table:** **Table 2.** Clinical Characteristics of Eligible Subjects

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### Heart Rate Variability and Cardiac Events

Table 3 ✦ shows mean values ( $\pm$ SD) for eight heart rate variability measures separately for men and women. The mean duration of processed time for analyses was 94 minutes (range, 33 to 120 minutes), corresponding to 56 100-s blocks.

**View this table:** **Table 3.** Heart Rate Variability Measures

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During a mean follow-up of 3.5 years (range, 4 days to 6.4 years), there were 58 new cardiac events. The initial event was angina pectoris in 22 subjects, coronary insufficiency in 1,

recognized myocardial infarction in 20, unrecognized myocardial infarction in 2, death of coronary heart disease in 5, and congestive heart failure in 8.

Rates for cardiac events according to tertiles of each heart rate variability measure are presented in Table 4\*. Two-hour SDNN, very-low-frequency power, low-frequency power, and total power demonstrated strikingly higher event rates among subjects in the lowest tertile. Approximately two thirds of cardiac events occurred in subjects in the bottom tertile, whereas only ≈10% of the outcomes occurred in subjects in the top tertile.

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**Table 4.** Cardiac Event Rates as a Function of Sex-Specific Tertiles of Each Heart Rate Variability Measure

Table 5\* lists hazard ratios for subsequent cardiac events per 1-SD decrement of all eight heart rate variability measures analyzed separately. In age- and sex-adjusted analyses, 2-hour SDNN, very-low-frequency power, low-frequency power, and total power were significantly associated with increased risk for cardiac events; each had a hazard ratio of ≈1.4.

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**Table 5.** Proportional Hazards Regression Analysis of the Impact of Heart Rate Variability Measures on Incidence of Cardiac Events

In the stepwise analyses to determine relevant clinical risk factors, frequent supraventricular premature beats ( $\geq 120/h$ ), smoking, diabetes, systolic blood pressure, left ventricular hypertrophy on ECG, diuretic use,  $\beta$ -blocker use, other cardiac medication use, and mean heart rate were each associated with subsequent cardiac events. Therefore, they were included in multivariate proportional hazards models. All heart rate variability measures except the ratio of low-frequency to high-frequency power revealed significant associations with subsequent cardiac events after adjustment for the clinical risk factors. The highest hazard ratio was 1.47 for 2-hour SDNN.

Additional multivariate analyses were performed incorporating total cholesterol and the ratio of total to HDL cholesterol; these analyses were based on 560 original subjects and 1828 Offspring Study participants. Hazard ratios for cardiac events per 1-SD increment of each heart rate variability measure are shown in the bottom third of Table 4 <sup>♣</sup>.

Mean heart rate was significantly associated with risk for cardiac events after adjustment for age, sex, and clinical risk factors ( $P=.04$ ). Because it was correlated with heart rate variability measures<sup>22</sup> and is a simple measure of autonomic balance, mean heart rate subsequently was added to the multivariate models along with sex, age, and clinical risk factors. After we adjusted for mean heart rate and clinical variables, 2-hour SDNN was the only heart rate variability measure significantly related to risk for cardiac events; a 1-SD decrement in 2-hour SDNN was associated with a hazard ratio of 1.41 (95% CI of 1.05 to 1.89;  $P=.0216$ ).

Because there was less objective evidence to substantiate diagnoses of angina and unrecognized myocardial infarction, we performed secondary analyses of "hard" end points (coronary insufficiency, recognized myocardial infarction, deaths from coronary heart disease, and congestive heart failure [ $n=40$ ]). These analyses revealed that the hazard ratios of all eight heart rate variability measures, adjusted for age and sex, were higher than their corresponding associations in the primary analyses. The highest hazard ratio was 1.65 for 2-hour SDNN with a 95% CI of 1.28 to 2.12 ( $P=.0001$ ).

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## Discussion

In this study of 2501 men and women who were free of clinically apparent heart disease, reduced heart rate variability predicted increased risk for subsequent cardiac events. These findings may provide insight into the prognostic implications of altered heart rate variability.

We previously demonstrated that reduced heart rate variability predicted increased risk for all-cause mortality.<sup>22</sup> The present investigation differs from our earlier study in several key aspects. Our earlier report<sup>22</sup> was based on 736 subjects (mean age, 72 years) from the original Framingham Heart Study cohort, whereas the current report is based on 2501 subjects (mean age, 53 years) from the original Framingham Heart Study cohort and from the Framingham Offspring Study. Fewer than 30% of subjects in the current report were included in the earlier investigation. The end points were different in the two reports; the prior study only examined all-cause



mortality (only 18 of 74 deaths were due to coronary heart disease). In the present investigation, the end point was coronary disease or congestive heart failure (n=58); there were only 5 fatal end points. In addition, subjects in the current investigation were excluded if they had evidence of prior coronary disease or congestive heart failure.

The biological mechanism explaining our present results remains unknown. Heart rate variability is a marker of sympathetic and parasympathetic influences on the modulations of heart rate.<sup>32</sup> In patients with heart disease, increased sympathetic tone and/or decreased parasympathetic tone, which predispose to ventricular fibrillation, have been proposed as mechanisms explaining the associations of reduced heart rate variability with increased mortality.<sup>15 16</sup> However, our subjects were free of clinically apparent cardiac disease at baseline, and the vast majority of our outcomes were not arrhythmic (eg, sudden death); hence, it is difficult to attribute our results to autonomic imbalance precipitating fatal arrhythmic events. Rather, other factors such as cardiac chronotropic responsiveness may play an important role. In this sense, reduced heart rate variability may reflect subclinical cardiac disease. Alternatively, autonomic imbalance or other factors related to heart rate variability, such as the renin-angiotensin system,<sup>1 33</sup> may contribute to the pathogenesis of coronary heart disease,<sup>34</sup> but this hypothesis requires additional support.

Mean heart rate reflects autonomic balance and correlates inversely with all eight heart rate variability measures.<sup>22</sup> Although adjustment for mean heart rate may reduce the inherent predictive value of heart rate variability as an indicator of autonomic tone, 2-hour SDNN remained predictive of prognosis even after adjustment for mean heart rate. Two reasons for this can be considered. First, heart rate variability is a more sensitive tool for detecting autonomic balance than mean heart rate. Second, heart rate variability reflects additional information beyond autonomic imbalance.

This report is based on use of daytime 2-hour ambulatory ECG recordings for heart rate variability. Recordings were obtained during an active clinic visit; the results of basal, resting recordings likely would be different. Although the short-term nature of the recordings may have influenced heart rate variability measures, Bigger and coworkers<sup>35</sup> reported that frequency-domain analyses computed from 2- to 15-minute segments were not meaningfully different from those calculated for 24 hours, and they remained predictive of mortality regardless of the time of day. On the other hand, the SD of normal RR intervals increases as a function of the recording duration.<sup>36</sup> The SD of normal RR intervals from 24-hour recordings is predictive of mortality<sup>15</sup> and strongly correlates with low-frequency power, very-low-frequency power, and ultralow-frequency power,<sup>22 37</sup> which are predictors of mortality in frequency-domain analyses.<sup>16 17 19</sup> The SD of normal RR intervals is a simple measure of heart rate variability. On the basis of the present study, it would appear that the SD of normal RR intervals calculated from 2 hours of ambulatory recording may suffice to assess risk for clinical outcomes, and it was the superior predictor of outcome among the eight heart rate variability measures studied.

A few limitations of the present study should be addressed. First, the number of outcomes was too small to assess the relations of heart rate variability measures to individual cardiac end points. Nevertheless, secondary analyses of hard cardiac outcomes demonstrated higher hazard ratios for all eight heart rate variability measures than in primary analyses, thereby suggesting a stronger association of heart rate variability with risk for more rigorously defined and objective end

points. Second, this investigation was based on a relatively healthy sample because of the exclusion of subjects with frequent arrhythmias, a history of coronary heart disease or congestive heart failure, and those who did not attend the index examination. Third, because of the 100-s block method we used, the lower limit of the frequency-domain variables was 0.01 Hz. Additionally, the time-domain analyses were based on 2 hours of data; the values obtained from short-term recordings will differ from those based on longer periods of observation. Last, the ability to predict future cardiac events by use of only heart rate variability measures is limited; a 1-SD decrement in 2-hour SDNN reflects an  $\approx$ 50% increase in risk of cardiac events over the next 3.5 years. In the present study, this equates to the same risk increase estimated for an 8-year age increment, or approximately one half the increase associated with diabetes or smoking.

This is the first prospective study to identify an association between heart rate variability and heart disease risk in a community-based population. The estimation of heart rate variability by ambulatory ECG monitoring offers prognostic information beyond that provided by the evaluation of traditional cardiovascular risk factors.



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